

**REMARKS**

Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, and 27-37 were pending and considered in the last Office Action dated January 4, 2005. Claims 28, and 35-37 have been canceled, and claims 1, 2, 10, 11, 19, and 20 have been amended herein. No new matter is introduced by these amendments. Amendments to claims 2, 11 and 20 provide correction of a minor grammatical error. Amendments to independent claims 1, 10 and 19 are presented in the interests of facilitating prosecution following the Examiner's final rejection of all the claims. These amendments are made without disclaimer or prejudice.

Support for the amendments to claims 1, 10 and 19 can be found throughout the application as filed. For example, support for the amendments providing an oligonucleotide "that is from about 5 to about 100 nucleotides in length" can be found at page 8, lines 23-27. Furthermore, support for the amendments providing that "statistical significance is determined using an unpaired t-test and p is less than or equal to 0.08 when the method is compared to a control in which either no prodrug is administered or no oligonucleotide is administered" can be found, for example, in Applicants' previously presented claim 38, as well as at pages 13 and 14.

Applicants' detailed response follows. This response and amendment after final rejection addresses the Examiner's remaining bases for rejection and provides amendments which place the application in better condition for allowance.

**Information Disclosure Statement**

Applicants gratefully acknowledge that their Information Disclosure Statement filed on October 18, 2004 has now been entered and the references referred to therein have now been considered on their merits.

Specification

Applicants gratefully acknowledge that their amendments to the specification to replace “CAMPOTOSAR” with the generic term “irinotecan” have now been entered.

Claim Objections

Applicants gratefully acknowledge that their amendment to claim 10 to remove the second occurrence of the word “the” in line 3 has been entered and the objection to claim 10 has been withdrawn accordingly.

Rejections under 35 U.S.C. §112, 2<sup>nd</sup>

The Office Action states that claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, and 27-37 remain rejected under 35 U.S.C. §112, 2<sup>nd</sup> paragraph, as being indefinite “for the reasons of record set forth in the previous Office Action mailed May 14, 2004.” On this point that previous Action states that “[w]ithout a specific definition of what is ‘statistically significant’, one of ordinary skill in the art is not apprised of the metes and bounds of the claim.”

For the record, Applicants maintain that the language “statistically significant” is definite, because the skilled artisan is familiar with the applicable tests for statistical significance and such tests are fully exemplified within the teachings of Applicants’ specification. Further to this point, Applicants note that the examination guidelines for clarity and precision under 35 U.S.C. §112, 2<sup>nd</sup> provide that “(the examiner) should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness” (MPEP §2173.02). Furthermore, these examination guidelines clearly provide that “[d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of....[t]he content of the particular application disclosure; [t]he teachings of the prior art; and [t]he claim interpretation that would be given by

one possessing the ordinary level of skill in the pertinent art at the time the invention was made” ( emphasis added, MPEP §2173.02). As provided in Applicants’ earlier responses, these considerations clearly allow that the claim terminology “statistically significant” is adequately particular and distinct, and thereby definite under 35 U.S.C. §112, 2<sup>nd</sup>.

Nevertheless, in the interest of facilitating prosecution and not in acquiescence to this rejection, Applicants have amended independent claims 1, 10 and 19 to provide that the statistical significance “is determined using an unpaired t-test and p is less than or equal to 0.08 when the method is compared to a control in which either no prodrug is administered or no oligonucleotide is administered.” The remaining claims that were rejected on these grounds depend from claims 1, 10 or 19, and, accordingly, the amendment of claims 1, 10 and 19 applies to them as well.

In view of these amendments that directly address the asserted basis for the rejection, Applicants respectfully believe that no basis for the rejection for lack of claim definiteness remains. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102

The Office Action states that the rejection of claims 1, 2, 5, 10, 11, 14, 19, 20 and 23 under 35 U.S.C. §102(b) in view of Koike *et al.* ((1997) Cancer Research 57: 5475-79) has been maintained for the reasons of record set forth in the previous Office Action mailed May 14, 2004. In particular, the Office Action states “that the instant specification does not provide a definition of an oligonucleotide...[t]herefore, given its broadest reasonable interpretation, the oligonucleotide of the instant claims can be any size, including the 805bp fragment taught by Koike *et al.*”

Applicants respectfully disagree. The requirement that claims be given “their broadest reasonable interpretation” is in conflict with such a construction, because it requires that an

approximately 805 nucleotide long, endogenously-synthesized antisense transcript fall within the meaning of the term “oligonucleotide”. This construction is not reasonable, and, indeed utilizes a meaning for the term “oligonucleotide” that is repugnant to its ordinary meaning. In particular, it is well known in the art that the term “oligonucleotide” encompasses only relatively short polynucleotide chains, as provided in the specification, of anywhere from about 5 to about 100 nucleotides in length. Above this length the term “polynucleotide” is generally used. Indeed, the root “oligo” specifically means “few” (see, *e.g.*, Webster’s Ninth Collegiate Dictionary). Accordingly, the term “oligonucleotide” is understood to mean “a relatively short single-stranded nucleic acid chain” (see Exhibit A, taken from Merriam Webster’s Medical Desk Dictionary, Merriam-Webster, Inc. Publishers, Springfield Massachusetts, copyright 2002).

Accordingly, Applicants respectfully aver that a common and reasonable construction of the term “oligonucleotide” in claims 1, 10 and 19 precludes a finding of anticipation by Koike *et al.*, which teaches an 805 nucleotide antisense transcript that is synthesized *in situ* from a transfected recombinant vector.

Notwithstanding Applicants’ belief in the merits of their position, and solely in the interest of facilitating prosecution, Applicants have amended independent claims 1, 10 and 19 without prejudice to specify that the claimed method utilizes an oligonucleotide “that is from about 5 to about 100 nucleotides in length,” as supported in the application at page 8, lines 23 to 27. Applicants respectfully aver that this amendment obviates any possible issue with regard to the Koike *et al.* reference under 35 U.S.C. §102(b).

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Rejections under 35 U.S.C. §103

The Office Action states that the rejection of claims 1-6, 8-15, 17-24, 26 and 27 under 35 U.S.C. §103(a) has been maintained for the reasons of record. In particular, the Office Action

states that, as provided previously in the rejection under 35 U.S.C. §102(b) in view of Koike *et al.*, “given the broadest reasonable interpretation, the oligonucleotide of the instant claims can be any size, including the 805 (nucleotide transcript) taught by the Koike *et al.* reference”.

Applicants respectfully aver that their amendment specifying that the claimed method utilizes an oligonucleotide “that is from about 5 to about 100 nucleotides in length,” obviates this rejection. Indeed, there would have been no motivation, and indeed none has been presented, to modify the 805 bp antisense transcript inferable from the teachings of Koike *et al.* to an “oligonucleotide that is from about 5 to about 100 nucleotides in length,” to arrive at the claimed invention.

Furthermore, when assessing the differences between the prior art and the claimed invention as a part of the Graham factual inquiries relevant to patentability under 35 U.S.C. §103 (see MPEP §2141), it is critical the claimed invention as a whole, including inherent properties of the claimed invention, be considered (see MPEP §2141.02). In this regard, Applicants note that there would have been no motivation, and indeed no argument has been presented, to modify the gene-specific antisense cMOAT transcript inferable from the Koike *et al.* reference to arrive at the inherently sequence-independent oligonucleotides of the instant claimed invention. Indeed, having established that the teachings of the Koike *et al.* reference are clearly outside the scope of the claimed invention, the fact that the claimed invention provides a method utilizing oligonucleotides of no particular sequence specificity must be considered in assessing whether the skilled artisan, in view of the teachings of Koike *et al.* (and/or Baracchini *et al.*), would have been motivated to modify the prior art to arrive at the claimed invention. The inevitable conclusion is that there would have been no such motivation to modify the teachings of the cited art to arrive at the claimed invention, because one of skill in the art would have considered oligonucleotides that were not specific to endogenous host target genes to be biologically ineffective in the claimed co-treatment method with an SN-38 prodrug. Nothing within the teachings of Koike *et al.* (or Baracchini *et al.*) teaches or suggests otherwise.

In this regard, Applicants note that one of the critical contributions provided by the instant invention is the recognition of a beneficial, sequence-independent chemotherapeutic potentiation of SN-38 prodrugs by oligonucleotides. Indeed, prior to Applicants invention, such sequence non-specific oligonucleotides were used as negative controls in antisense experiments (see, *e.g.*, Example 1 of the Chen *et al.* patent U.S. 6,013,786, which was previously cited in this application by the Examiner). Accordingly, one of skill in the art would have had no reasonable expectation of success in modifying the sequence-specific antisense transcript inferable from the Koike *et al.* reference to arrive at the claimed invention utilizing sequence-independent oligonucleotides.

Applicants emphasize that, while the instant claims allow for sequence independent oligonucleotides, but do not specifically require that the oligonucleotides utilized are necessarily non-targeting so that the claimed class would therefore include such gene-homologous structures, still the sequence independence is relevant to the assessment of the claimed invention as a whole and its inventive distance from the teachings of the prior art under 35 U.S.C. §103. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

The Office Action further states that claims 1, 10, 19, and 35-37 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Office Action states “Applicant’s specification only teaches CPT-11, but does not provide a sufficient number of representative species of the genus of CPT-11 analogs, which would allow one of skill in the art to predict the structures of all members of the claimed genus.” Applicants respectfully disagree for the reasons that follow.

As an initial matter, Applicants note that the written description requirement is applied to the claimed invention, and the instant rejected independent claims 1, 10 and 19 are directed to

methods of use of SN-38 prodrugs, and not specifically “CPT-11 analogs” as addressed by the Examiner’s rejection. Indeed, Applicants respectfully aver that the application as filed provides exemplary written description support for this claimed class of SN-38 prodrugs. In particular, at page 6, lines 10-22, the specification provides that

“preferred active compounds (include) SN-38...(and)... [t]he moiety that is cleaved from the prodrug may preferably be selected from esters and alpha-acyloxyalkyl esters (for carboxy functionalities); amides esters, carbonate esters, phosphate esters, esters and alpha-acyloxyalkyl ethers (for hydroxy functionalities); thioesters, alpha-acyloxyalkyl thioesters and disulfides (for sulfhydryl functionalities); ketals, imines, enol esters, oxazloadines, and thiazolidines (for carbonyl functionalities); amides, carbamates, imines enamines N-Mannich bases, and N-acyloxyalkoxycarbonyl derivatives (for amino functionalities); N-acyloxyalkyl derivatives (for quarternary amino functionalities); N-sulphonyl imidates (for ester or sulfonamide functionalities); N-Mannich bases (for NH-acidic functionalities); and N-acyloxyalkyl derivatives (for heterocyclic amino functionalities).”

Applicants aver that this detailed description of chemical moieties that may be used to modify SN-38 to obtain the various prodrug forms of SN-38 provides a precise and definite description of the claimed genus “in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention” (see MPEP §2163, I.). The prodrug forms of SN-38 described in the application includes irinotecan (CPT-11), which is an exemplary ester-modified SN-38 prodrug. In view of the fact that this genus of SN-38 prodrugs is supported in detail in the application as filed, Applicants’ respectfully request reconsideration and withdrawal of the rejection of independent claims 1, 10 and 19 for lack of written description.

Further in this regard, the remaining claims that have been rejected for lack of written description, *i.e.* dependent claims 35-37, are directed to methods of use of a “CPT-11 analog”. Applicants respectfully aver that, contrary to the assertions in the Office Action, the genus of CPT-11 analogs would be recognized by the skilled artisan in light of Applicants’ teachings. In particular, the specification adequately describes CPT-11 as well as CPT-11 analogs. The

structure of such irinotecan (CPT-11) was known in the art at the time of the invention. Furthermore, the skilled artisan, reading in light of the teachings of the specification, would recognize that claims 35-37 are directed to CPT-11 analogs that: (i) release SN-38 and thus are "SN-38 prodrugs"; and (ii) are chemical analogs of CPT-11 that are chemically similar to CPT-11 (irinotecan) and which come within the detailed chemical description of SN-38 prodrugs taught by the specification (as provided above).

Applicants respectfully note that there is no need to disclose that which is well known in the art, or that which would be understood by the person of skill in the art in view of the teachings of the specification. Indeed, the instant specification provides more than adequate disclosure of the claimed "CPT-11 analogs" for a person of skill in the art to recognize that Applicants were in possession of the claimed invention at the time of filing.

Nevertheless, in an effort to facilitate prosecution, and not in acquiescence to the rejection, Applicants have canceled claims 35-37, which contain the "CPT-11 analog" language cited in this rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

### **CONCLUSION**

In view of the amendments to the claims and the arguments presented above, Applicants respectfully aver that all of the claims are in condition for allowance, and reconsideration and notification of such is hereby respectfully requested. The time for responding to the Action has been extended to June 4, 2005 by the accompanying Petition for a Two-Month Extension of Time and authorization to charge the associated fee due.

Although no other fees are believed due at this time, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. 08-0219.



APPL. NO. 09/708,786  
REPLY TO OFFICE ACTION OF  
JANUARY 4, 2005

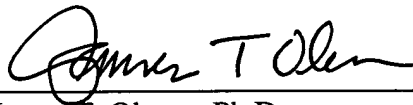
ATTY. DOCKET NO. 47508.700US2 (HYZ-700US2)

If the Examiner believes that a telephone conference would expedite this matter, the Examiner is respectfully requested to telephone the applicant's undersigned attorney at (617) 526-6045.

Respectfully submitted,

WILMER CUTLER PICKERING HALE AND  
DORR LLP

Date: June 2, 2005

A handwritten signature in black ink, appearing to read "James T. Olesen", is written over a horizontal line.

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EXHIBIT A

# Merriam-Webster's Medical Desk Dictionary



MERRIAM-WEBSTER, INCORPORATED, *Publishers*  
Springfield, Massachusetts, U.S.A.



### A GENUINE MERRIAM-WEBSTER

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gone, and that is well developed in most vertebrates but is reduced to a narrow elongated body in humans

**olfactory nerve** *n*: either of the pair of nerves that are the first cranial nerves, that serve to conduct sensory stimuli from the olfactory organ to the brain, and that arise from the olfactory cells as discrete bundles of unmyelinated fibers passing in small groups (in humans, about 20) through the cribriform plate of the ethmoid bone and terminating in the olfactory bulb — called also *first cranial nerve*

**olfactory organ** *n*: an organ of chemical sense that receives stimuli interpreted as odors from volatile and soluble substances in low dilution, that lies in the walls of the upper part of the nasal cavity, and that forms a mucous membrane continuous with the rest of the lining of the nasal cavity and made up of tall columnar sustentacular cells containing golden brown pigment interspersed with olfactory cells the outer processes of which project between the sustentacular cells as small vesicles surmounted by delicate sensory filaments and the inner ends of which are continuous with fibers of the olfactory nerves

**olfactory pit** *n*: a depression on the head of an embryo that becomes converted into a nasal passage — called also *nasal sac*

**olfactory placode** *n*: a thick plate of cells derived from the neural ectoderm in the head region of the vertebrate embryo and developing into the olfactory region of the nasal cavity

**olfactory tract** *n*: a tract of nerve fibers in the olfactory lobe on the inferior surface of the frontal lobe of the brain that passes from the olfactory bulb to the olfactory trigone

**olfactory trigone** *n*: a triangular area of gray matter on each side of the brain forming the junction of an olfactory tract with a cerebral hemisphere near the optic chiasma

**olfactory tubercle** *n*: a small area of gray matter behind the olfactory trigone that is noted for receiving dopaminergic neurons from the substantia nigra and the reticular formation which have been implicated in schizoaffective disorders.

**olfac-ty** \äl-'fak-tē, ōl-\ *n*, *pl* -ties: an arbitrary unit used in olfactometry for measuring the strength of an odorous stimulus

**olib-a-num** \ō-'lib-ə-nəm\ *n*: FRANKINCENSE

**ol-i-ge-mia** or chiefly *Brit* **ol-i-gae-mia** \äl-ə-'gē-mē-ə, -'jē-\ *n*: a condition in which the total volume of the blood is reduced — **ol-i-ge-mic** or chiefly *Brit* **ol-i-gae-mic** \-mik\ *adj*

**oli-go** \äl-i-gō, 'ō-li-\ *n*: OLIGONUCLEOTIDE

**oli-go-ar-tic-u-lar** \äl-i-gō-är-'tik-yə-lar, ə-'lig-ə-\ *adj*: affecting a few joints (<~ arthritis) — compare MONOARTICULAR, POLYARTICULAR

**oli-go-chro-me-mia** or chiefly *Brit* **oli-go-chro-mae-mia** \krō-'mē-mē-ə\ *n*: deficiency of hemoglobin in the blood

**oli-go-clon-al** \-'klōn-əl\ *adj* 1: cloned or derived from one or a few cells or molecules (<~ T cells) (<~ lymphomas) 2: of, relating to, or being any small group of proteins that migrate close together during electrophoresis producing closely placed bands on the electrophoretogram (<~ immunoglobulins) — **oli-go-clo-nal-i-ty** \-klō-'nal-ət-ē\ *n*, *pl* -ties

**oli-go-cy-the-mia** or chiefly *Brit* **oli-go-cy-thae-mia** \-'si-'thē-mē-ə\ *n*: deficiency in the total number of red blood cells present in the body — compare ANEMIA 1 — **oli-go-cy-the-mic** or chiefly *Brit* **oli-go-cy-thae-mic** \-'thē-mik\ *adj*

**oli-go-dac-tyl-ism** \-'dak-tə-'liz-əm\ *n*: the presence of fewer than five digits on a hand or foot

**oli-go-dac-ty-ly** \-'dak-tə-lē\ *n*, *pl* -lies: OLIGODACTYLISM

**oli-go-den-dro-cyte** \-'den-drə-'sīt\ *n*: a neuroglial cell resembling an astrocyte but smaller with few and slender processes having few branches

**oli-go-den-drog-lia** \-'den-'dräg-lē-ə, -'drög-\ *n*: neuroglia made up of oligodendrocytes that is held to function in myelin formation in the central nervous system — **oli-go-den-drog-li-al** \-lē-əl\ *adj*

**oli-go-den-dro-gli-o-ma** \-'den-drō-glī-'ō-mə\ *n*, *pl* -mas or -ma-ta \-mə-tə\ *n*: a tumor of the nervous system composed of oligodendroglia

**oli-go-de-oxy-nu-cle-o-tide** \-(j)de-'äk-sē-'n(y)ü-klē-ə-'tīd\ *n*: an oligonucleotide consisting of deoxyribose-containing nucleotides

**oli-go-de-oxy-ri-bo-nu-cle-o-tide** \-'rī-bō-'n(y)ü-klē-ə-'tīd\ *n*: OLIGODEOXYNUCLEOTIDE

**oli-go-dy-nam-ic** \-dī-'nam-ik\ *adj* 1: active in very small quantities (<an ~ germicide) 2 a: produced by very small quantities (<~ action of finely divided silver in disinfecting water) b: of or relating to the action of such quantities 3: of, relating to, or being produced by the specific activity of an oligodynamic substance (<the ~ action of some pyridine derivatives on pathogenic microorganisms)

**oli-go-gene** \äl-i-gō-'jēn, ə-'lig-ə-\ *n*: a gene that exerts a major effect on a character either as one of two Mendelian alternatives or as one of a few genes controlling a qualitative character — **oli-go-gen-ic** \äl-i-gō-'jen-ik, ə-'lig-ə-, -'jē-nik\ *adj*

**oli-go-hy-dram-ni-os** \äl-i-gō-'hī-'dram-nē-ās, ə-'lig-ə-\ *n*: deficiency of amniotic fluid sometimes resulting in an embryonic defect through adhesion between embryo and amnion

**oli-go-lec-i-thal** \-'les-ə-thəl\ *adj*, of an egg: having little yolk (<echinoderm eggs are ~)

**oli-go-men-or-rhea** or chiefly *Brit* **oli-go-men-or-rhoea** \-'men-ə-'rē-ə\ *n*: abnormally infrequent or scanty menstrual flow

**oligo-mer** \ə-'lig-ə-mər\ *n*: a polymer or polymer intermediate containing relatively few structural units — **oligo-mer-ic** \-'lig-ə-'mer-ik\ *adj* — **oligo-mer-iza-tion** \-mə-rə-'zā-shən\ *n*

**oli-go-my-cin** \äl-i-gō-'mīs-'n, 'ō-li-\ *n*: any of several antibiotic substances produced by an actinomycete of the genus *Streptomyces* (*S. diastatochromogenes* or a closely related species) and used esp. in biochemical research to inhibit oxidative phosphorylation

**oli-go-nu-cle-o-tide** \-'n(y)ü-klē-ə-'tīd\ *n*: a relatively short single-stranded nucleic-acid chain (as an oligodeoxynucleotide or oligoribonucleotide) usu. consisting of up to approximately 20 nucleotides

**oli-go-pep-tide** \äl-i-gō-'pēp-'tīd, -'pē-lē-\ *n*: a protein fragment or molecule that usu. consists of less than 25 amino acid residues linked in a polypeptide chain

**oli-go-phre-nia** \-'frē-nē-ə\ *n*: MENTAL RETARDATION

**oli-go-phren-ic** \-'frē-nik\ *adj*: of, relating to, or exhibiting mental retardation

**oligophrenic** *n*: a mentally retarded individual

**oli-go-ri-bo-nu-cle-o-tide** \-'rī-bō-'n(y)ü-klē-ə-'tīd\ *n*: an oligonucleotide consisting of ribonucleotides

**oli-go-sac-cha-ride** \äl-i-gō-'sak-ə-'rīd, 'ō-li-\ *n*: a saccharide (as a disaccharide) that contains a known small number of monosaccharide units

**oli-go-si-a-lia** \-'si-'ā-lē-ə\ *n*: an abnormal deficiency of saliva

**oli-go-sper-mia** \-'spər-mē-ə\ *n*: deficiency of sperm in the semen — **oli-go-sper-mic** \-'spər-mik\ *adj*

**oli-go-trich-ia** \-'trik-ē-ə\ *n*: deficiency in the growth of hair esp. when congenital

**ol-i-gu-ria** \äl-ə-'g(y)ūr-ē-ə\ *n*: reduced excretion of urine — **ol-i-gur-ic** \-ik\ *adj*

**ol-i-vary** \äl-ə-'ver-ē\ *adj* 1: shaped like an olive 2: of, relating to, situated near, or comprising one or more of the olives, inferior olives, or superior olives (the ~ complex) (<~ fibers)

**olivary body** *n*: OLIVE 2

**olivary nucleus** *n* 1: INFERIOR OLIVE 2: SUPERIOR OLIVE  
**ol-ive** \äl-iv, -əv\ *n* 1: an Old World evergreen tree (*Olea europaea* of the family Oleaceae, the olive family) cultivated for its drupaceous fruit that is an important food and source of oil; also: the fruit 2: an oval eminence on each ventrolateral aspect of the medulla oblongata that contains the inferior olive of the same side — called also *olivary body*

**olive oil** *n*: a pale yellow to yellowish green nondrying oil obtained from the pulp of olives usu. by expression and used

chiefly as a salar emollient

**ol-i-vo-cere-bel-** ing to the cereb  
**olivocerebellar** olive on one sid  
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**ol-i-vo-pon-to-cc**  
är-\ *n*: an inhe  
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degeneration

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**oma-si-tis** \ō-m

**oma-sum** \ō-'mā  
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**ome-ga-3** \-'thri  
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carbon chain b  
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acid group and  
oils, and green

**omenta** *pl* of OM

**omen-tal** \ō-'me  
omentum

**omen-tec-to-my**  
resection of all

**omen-to-pexy** \-  
tion of suturing

**omen-to-plasty**  
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**omen-tor-rha-pl**  
repair of an om

**omen-tum** \ō-'m  
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the viscera) —

**omen-tum-ec-to**  
: OMENTECTOMY

**omep-ra-zole** \-  
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flux, erosive es

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**om-ni-fo-cal** \äi  
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**om-niv-o-rous** \-  
plant matter —

*n*

**omo-hy-oid** \ō-  
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**omohyoid musc**

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